

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Zhou, KX; Bellenguez, C; Spencer, CCA; Bennett, AJ; Coleman, RL; Tavendale, R; Hawley, SA; Donnelly, LA; Schofield, C; Groves, CJ; +40 more... Burch, L; Carr, F; Strange, A; Freeman, C; Blackwell, JM; Bramon, E; Brown, MA; Casas, JP; Corvin, A; Craddock, N; Deloukas, P; Dronov, S; Duncanson, A; Edkins, S; Gray, E; Hunt, S; Jankowski, J; Langford, C; Markus, HS; Mathew, CG; Plomin, R; Rautanen, A; Sawcer, SJ; Samani, NJ; Trembath, R; Viswanathan, AC; Wood, NW; Harries, LW; Hattersley, AT; Doney, ASF; Colhoun, H; Morris, AD; Sutherland, C; Hardie, DG; Peltonen, L; McCarthy, MI; Holman, RR; Palmer, CNA; Donnelly, P; Pearson, ER; (2011) Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. *Nature genetics*, 43 (2). 117-U57. ISSN 1061-4036 DOI: <https://doi.org/10.1038/ng.735>

Downloaded from: <http://researchonline.lshtm.ac.uk/1304/>

DOI: <https://doi.org/10.1038/ng.735>

Usage Guidelines:

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

Supplementary Information

Common variants near *ATM* are associated with glycaemic response to metformin in type 2 diabetes

Kaixin Zhou*, **Celine Bellenguez***, **Chris Spencer**, **Amanda J Bennett**, **Ruth L Coleman**, **Roger Tavendale**, **Simon A Hawley**, **Louise Donnelly**, **Chris Schofield**, **Christopher J Groves**, **Lindsay Burch**, **Fiona Carr**, **Amy Strange**, **Colin Freeman**, **Jenefer M Blackwell**, **Elvira Bramon**, **Matthew A Brown**, **Juan P Casas**, **Aiden Corvin**, **Nicholas Craddock**, **Panos Deloukas**, **Serge Dronov**, **Audrey Duncanson**, **Sarah Edkins**, **Emma Gray**, **Sarah Hunt**, **Janusz Jankowski**, **Cordelia Langford**, **Hugh S Markus**, **Christopher G Mathew**, **Robert Plomin**, **Anna Rautanen**, **Stephen J Sawcer**, **Nilesh J Samani**, **Richard Trembath**, **Ananth C Viswanathan**, **Nicholas W Wood**, **MAGIC investigators**, **Lorna W Harries**, **Andrew Hattersley**, **Alex SF Doney**, **Helen Colhoun**, **Andrew D Morris**, **Calum Sutherland**, **D. Grahame Hardie**, **Leena Peltonen**, **Mark I McCarthy**, **Rury R. Holman**, **Colin N.A. Palmer[†]**, **Peter Donnelly[†]**, **Ewan R Pearson[†]**

* These authors contributed equally to this work

† These authors jointly supervised this work

Correspondence should be addressed to: e.pearson@cpse.dundee.ac.uk

SUPPLEMENTARY TABLES**Supplementary Table 1**

Baseline characteristics of discovery (GoDARTS) and replication Cohorts (GoDARTS and UKPDS). Data are mean \pm SD.

Variable	Discovery GoDARTS (1024)	Replication 1 GoDARTS (1783)	Replication 2 UKPDS (1113)
Age	62.8 \pm 9.8	61.0 \pm 11.7	57.5 \pm 9.6
Male Percentage	54.9%	57.7%	53.2%
BMI	31.5 \pm 5.7	31.9 \pm 5.9	30.2 \pm 5.9
Baseline A1c	8.94 \pm 1.38	8.95 \pm 1.37	8.43 \pm 1.93
Adherence	82.9 \pm 16.1	82.3 \pm 16.1	NA
Creatinine Clearance	89.1 \pm 31.3	96.7 \pm 37.4	95.9 \pm 34.0
Responder Percentage	53.7%	51.4%	35.2%
Monotherapy Percentage	67.3%	72.4%	25.5%

Supplementary Table 2

SNPs associated with metformin response in logistic regression analysis (with p-value $<10^{-4}$). 'EffAllele' (effective allele) is based on the dbSNP plus strand coding; 'Gene' covers any gene within 50kb vicinity of the SNP

CHR	SNP	POSITION	EffAllele	OR	P	Gene
1	rs12128858	34496515	C	0.5071	2.01E-05	<i>C1orf94</i>
1	rs7533876	102883521	A	0.5062	5.17E-06	
1	rs41404544	110944334	C	0.4341	5.58E-05	<i>KCNA2</i>
1	rs265128	215683383	A	0.5853	8.31E-05	<i>GPATCH2</i>
2	rs737447	44959521	G	1.798	3.29E-05	
2	rs4952726	44961125	C	1.793	3.73E-05	
2	rs13420376	144288475	T	1.898	1.37E-05	<i>ARHGAP15</i>
3	rs41521446	2808324	G	0.6114	5.22E-05	<i>CNTN4</i>
3	rs1963348	64190295	A	0.6701	8.94E-05	<i>PRICKLE2</i>
3	rs3911778	64205473	A	0.6678	8.03E-05	<i>PRICKLE2</i>
3	rs7613991	69845276	T	0.6787	4.72E-05	<i>MITF</i>
3	rs9853615	135002671	G	1.56	6.85E-06	<i>TF SRPRB RAB6B</i>
3	rs1464937	135019345	C	1.493	4.99E-05	<i>TF SRPRB RAB6B</i>
3	rs12637089	141370658	T	0.5363	7.30E-05	<i>CLSTN2</i>
4	rs10007566	24677262	T	0.637	3.39E-06	<i>LGI2</i>
5	rs4701486	25563999	G	0.6456	4.83E-05	
5	rs3843467	55892132	T	1.606	9.91E-05	
5	rs13187208	121014320	A	0.5283	4.76E-05	
6	rs10485258	154155102	T	1.556	8.74E-05	
7	rs4540325	4718366	T	0.6288	2.04E-06	<i>FOXK1</i>
7	rs2214096	95521055	G	1.561	6.28E-05	<i>DYNC111</i>
8	rs17741463	73163435	A	1.563	6.61E-05	<i>TRPA1</i>
8	rs1713669	96027813	G	0.6773	4.29E-05	<i>TP53INP1</i>
8	rs527234	96032974	G	0.6761	4.27E-05	<i>TP53INP1</i>
9	rs2274526	263233	C	0.6423	6.08E-05	<i>DOCK8</i>
9	rs10966249	2415127	T	1.493	4.78E-05	
9	rs7039085	2417960	A	1.511	5.72E-05	
9	rs2210396	2419859	C	1.502	6.71E-05	
9	rs2376118	2420189	G	1.514	5.93E-05	
9	rs16925655	7235728	T	0.4234	2.94E-06	
9	rs1928206	7265202	G	0.6011	2.64E-05	
9	rs16925783	7278704	A	0.4526	1.23E-05	
9	rs1008981	10536814	C	0.548	5.04E-06	<i>PTPRD</i>
9	rs957252	26049028	A	1.547	1.17E-05	
9	rs9406901	26052582	A	1.52	5.22E-05	
9	rs10984415	120923988	A	1.761	6.82E-05	<i>DBC1</i>
9	rs230150	120986331	C	1.756	2.66E-05	<i>DBC1</i>
9	rs230089	120995897	A	1.749	2.12E-05	<i>DBC1</i>
10	rs4750058	11508447	A	1.486	6.11E-05	<i>USP6NL</i>
10	rs7096907	19066847	T	0.5964	5.73E-05	
10	rs10763188	56681358	T	1.553	6.68E-05	
10	rs17123393	109565848	T	0.3917	3.96E-05	
11	rs875973	45083359	C	1.458	9.29E-05	<i>PRDM11</i>
11	rs12787445	107539334	G	1.604	8.81E-07	<i>ACAT1 NPAT</i>
11	rs6589007	107545314	A	1.635	2.69E-07	<i>ACAT1 NPAT</i>
11	rs2083707	107571340	A	1.589	1.80E-06	<i>ACAT1 NPAT ATM</i>
11	rs609557	107589723	G	1.632	2.47E-07	<i>NPAT ATM</i>
11	rs228606	107593057	T	0.6773	5.07E-05	<i>NPAT ATM</i>

Supplementary Table 2 (continued)

CHR	SNP	POSITION	EffAllele	OR	P	Gene
11	rs183460	107595920	A	1.631	2.98E-07	<i>NPAT ATM</i>
11	rs228591	107602543	A	1.632	2.65E-07	<i>NPAT ATM</i>
11	rs618499	107654049	A	1.585	1.49E-06	<i>ATM</i>
11	rs624366	107659307	G	1.648	1.69E-07	<i>ATM</i>
11	rs645485	107674073	A	1.638	2.37E-07	<i>ATM</i>
11	rs673281	107687279	G	1.579	1.95E-06	<i>ATM</i>
11	rs227073	107717902	G	1.622	4.06E-07	<i>ATM C11orf65</i>
11	rs227075	107723406	T	1.582	1.73E-06	<i>ATM C11orf65</i>
11	rs419716	107726309	A	1.633	2.85E-07	<i>ATM C11orf65</i>
11	rs227041	107728011	C	1.633	2.85E-07	<i>ATM C11orf65</i>
11	rs664143	107730871	A	1.582	1.73E-06	<i>ATM C11orf65</i>
11	rs652541	107731235	A	1.594	1.23E-06	<i>ATM C11orf65</i>
11	rs573890	107756573	C	1.625	3.90E-07	<i>ATM C11orf65</i>
11	rs227077	107758462	C	1.63	3.35E-07	<i>ATM C11orf65</i>
11	rs7931930	107773496	G	1.635	2.78E-07	<i>ATM C11orf65</i>
11	rs11212617	107788371	C	1.646	1.92E-07	<i>ATM C11orf65</i>
11	rs3765632	107858228	A	1.546	5.50E-06	<i>C11orf65 KDELC2 EXPH5</i>
11	rs11212676	107866788	A	0.6798	6.66E-05	<i>C11orf65 KDELC2 EXPH5</i>
11	rs893279	107870392	T	0.6864	9.68E-05	<i>C11orf65 KDELC2 EXPH5</i>
13	rs1328673	46513595	T	1.507	7.13E-05	
13	rs2039095	46516635	C	0.6871	9.83E-05	
13	rs9562700	46518957	A	0.6812	4.98E-05	
13	rs11148026	46538811	A	0.6746	4.11E-05	
13	rs1469595	46538887	A	0.6746	4.11E-05	
13	rs9595590	46540197	A	0.6746	4.11E-05	
13	rs7994733	46541595	C	1.503	8.40E-05	
13	rs1431768	46567351	A	1.501	8.37E-05	
13	rs9540636	65571144	T	0.6652	4.32E-05	
13	rs9540668	65623234	G	0.6759	6.74E-05	
15	rs2113931	59896761	A	0.5719	5.22E-05	<i>VPS13C</i>
16	rs4500723	51259514	T	1.499	4.08E-05	
16	rs4386133	51264345	A	1.467	8.04E-05	
16	rs12932515	51270048	T	1.474	8.91E-05	
16	rs11642888	51359637	C	1.47	5.96E-05	
16	rs7196680	51359682	C	1.461	7.78E-05	
17	rs9303683	30560283	A	0.6838	6.38E-05	<i>UNC45B AMAC1 SLFN5</i>
17	rs1383541	30563938	C	0.6549	8.67E-06	<i>UNC45B AMAC1 SLFN5</i>
17	rs11080325	30587822	A	0.6796	7.66E-05	<i>UNC45B AMAC1 SLFN5</i>
17	rs11653010	30589462	G	0.6812	8.52E-05	<i>UNC45B AMAC1 SLFN5</i>
18	rs1626048	3333266	A	2.016	5.53E-05	
18	rs1662830	3335173	G	2.037	4.76E-05	
18	rs9965202	75208922	C	0.5622	1.71E-05	<i>ATP9B NFATC1</i>
18	rs12604865	75211701	G	0.5612	1.83E-05	<i>ATP9B NFATC1</i>
18	rs6506757	75212528	T	0.5621	1.94E-05	<i>ATP9B NFATC1</i>

Supplementary Table 3

Full metformin glycaemic response models. The 95% confidence intervals of the Beta or Odds Ratio (OR) are shown in square brackets. The variables are coded as:

- (1) the outcome is Treatment A1c in linear model
- (2) the outcome is achieving treatment A1c \leq 7% (case) in logistic model
- (3) genotype is coded as the dosage of the minor allele
- (4) adherence is coded in 10%
- (5) creatinine CLR is coded in 10mL/min/1.73m²
- (6) group is coded as 1 for monotherapy group and 0 for dual therapy group
- (7) time to baseline is coded in months
- (8) dose is coded in 300mg

Supplementary Table 3a. The GWA cohort of 1024 GoDARTS patients

	Linear Model		Logistic Model	
	Beta	p	OR	p
rs11212617	-0.18 [-0.26,-0.10]	1.8E-05	1.64 [1.37,1.99]	1.9E-07
Baseline A1C	0.28 [0.23,0.32]	8.7E-33	0.69 [0.62,0.76]	3.3E-12
Adherence	-0.11 [-0.14,-0.07]	2.7E-8	1.18 [1.09,1.26]	4.3E-05
Creatinine CLR	0.04 [0.02,0.06]	2.3E-04	0.92[0.87,0.96]	0.0005
Group	-0.22 [-0.35,-0.09]	0.0011	1.97[1.47,2.64]	6.5E-06
Dose	-0.02 [-0.06,0.01]	0.18	0.99[0.96,1.02]	0.96
Baseline Gap	0.08 [0.006,0.14]	0.03	0.92[0.80,1.06]	0.23

Supplementary Table 3b. The first replication cohort of 1783 GoDARTS patients

	Linear Model		Logistic Model	
	Beta	p	OR	p
rs11212617	-0.07 [-0.13,-0.01]	0.022	1.21 [1.05,1.38]	0.007
Baseline A1C	0.20 [0.16,0.23]	2.7E-30	0.74 [0.69,0.80]	4.6E-14
Adherence	-0.11 [-0.14,-0.08]	2.6E-15	1.2 [1.14,1.26]	8.0E-10
Creatinine CLR	0.03 [0.01,0.04]	1.4E-05	0.95[0.92,0.98]	0.0003
Group	-0.32 [-0.43,-0.22]	6.5E-10	1.97[1.57,2.48]	3.8E-09
Dose	-0.03 [-0.06,-0.01]	0.02	1.01[0.98,1.04]	0.95
Baseline Gap	0.05 [-0.006,0.10]	0.09	0.90[0.79,1.03]	0.13

Supplementary Table 3c. The second replication cohort of 1113 UKPDS patients

	Linear Model		Logistic Model	
	Beta	p	OR	p
rs609261	-0.12 [-0.22,-0.02]	0.021	1.37 [1.10,1.72]	0.0057
Baseline A1C	0.50 [0.46,0.54]	4E-101	0.43 [0.39,0.49]	6.9E-45
Baseline Gap	-0.032[-0.03,-0.01]	5.5E-6	1.08 [1.03,1.14]	8.4E-4
Group	-0.93 [-1.13,-0.73]	8.2E-19	3.19[2.10,4.82]	4.2E-8
Treatment Gap	-0.01[-0.03,0.01]	0.214	1.01[0.97,1.06]	0.55
Creatinine CLR	0.05 [0.03,0.07]	1.6E-5	0.90[0.85,0.95]	1.0E-4

Supplementary Table 4

Logistic regression analysis of metformin response split by treatment group (monotherapy or dual therapy). The 95% confidence intervals of the Odds Ratio (OR) are shown in square brackets. The variables are coded as:

- (1) the outcome is achieving treatment A1c \leq 7% (case)
- (2) genotype is coded as the dosage of the minor allele
- (3) adherence is coded in 10%
- (4) creatinine CLR is coded in 10mL/min/1.73m²
- (5) time to baseline is coded in months
- (6) dose is coded in 300mg

Supplementary Table 4a. The GWA cohort of 1024 GoDARTS patients

	Monotherapy (n=689)		Dual therapy (n=335)	
	OR	p	OR	p
rs11212617	1.63 [1.29,2.06]	3.7E-05	1.71 [1.24,2.36]	0.001
Baseline A1C	0.66 [0.58,0.75]	1.7E-10	0.75 [0.62,0.91]	0.003
Adherence	1.18 [1.08,1.28]	6.0E-04	1.20 [1.03,1.40]	0.02
Creatinine CLR	0.93[0.87,0.98]	0.008	0.89[0.82,0.98]	0.02
Dose	0.99[0.93,1.07]	0.88	1.0[0.87,1.15]	0.95
Baseline Gap	0.95[0.87,1.10]	0.12	1.0[0.78,1.27]	0.98

Supplementary Table 4b The first replication cohort of 1783 GoDARTS patients

	Monotherapy (n=1291)		Dual therapy (n=492)	
	OR	p	OR	p
rs11212617	1.29 [1.10,1.51]	0.002	1.05 [0.81,1.36]	0.70
Baseline A1C	0.79 [0.72,0.86]	6.9E-08	0.60 [0.50,0.72]	2.8E-08
Adherence	1.20 [1.11,1.29]	1.3E-06	1.28 [1.12,1.46]	2.3E-04
Creatinine CLR	0.95[0.92,0.98]	0.001	0.94[0.88,1.01]	0.09
Dose	0.98[0.91,1.04]	0.52	1.05[0.94,1.18]	0.38
Baseline Gap	0.95[0.82,1.10]	0.51	0.81[0.64,1.02]	0.08

Supplementary Table 4c The second replication cohort of 1113 UKPDS

	Monotherapy (n=284)		Dual therapy (n=829)	
	OR	p	OR	p
rs609261	1.82 [1.20,2.78]	0.005	1.23 [0.94,1.62]	0.13
Baseline A1C	0.53 [0.43,0.65]	1.2E-09	0.39 [0.34,0.46]	3E-36
Baseline Gap	1.18 [1.03,1.35]	0.02	1.07 [1.02,1.12]	0.007
Treatment Gap	0.99[0.92,1.08]	0.92	1.02[0.97,1.07]	0.41
Creatinine CLR	0.83[0.75,0.90]	3.3E-5	0.94[0.88,1.01]	0.09

Supplementary Table 5

Association between rs11212617 and baseline characteristics in the Go-DARTS controls. The A allele was the reference allele. *These variables were log transformed.

Phenotype	Beta	N	p
LDL	-0.02671	6148	0.1186
Cholesterol	-0.01793	6148	0.3428
Triglycerides	0.00182	6148	0.8921
HDL	0.009234	6148	0.268
Creatinine	-0.1364	6148	0.7004
DBP	-0.1241	6148	0.4979
SBP	0.04596	6148	0.8966
Weight	-0.1744	6148	0.528
BMI	-0.07395	6148	0.377
Height	0.05636	6148	0.7474
A1C	-0.003857	6148	0.5882
Adiponectin*	0.02	2422	0.2555
Leptin*	0.0006	2422	0.9525
F-Insulin*	-0.04174	1806	0.0485
Homab*	-0.02116	1806	0.1317
Homas*	0.0418	1806	0.0474
F-Glucose*	-0.009783	1806	0.9525

Supplementary Table 6

Bioinformatic exploration of the functionality of rs11212617 and its proxies.

All the 98 SNPs with strong linkage disequilibrium ($r^2 > 0.8$ according to the HapMap CEU panel as indicated by the column rsquare in the table) to rs11212617 at the associated locus are listed in the table. SNPs were mapped to the genomic sequence with UCSC database checking their regulation potential, predicted transcription factor binding sites, CpG islands, predicted microRNA target sites, validated enhancer, promoter and cross species conservative sites.

In addition, none of the SNPs was identified as potential *cis* regulator in the three published eQTL genome wide association studies of liver, cortex and lymphocytes¹⁻³. The observed association could not be explained by the only common copy number polymorphism in the region as it is not in linkage disequilibrium with rs11212617 ($r^2 = 0.05$) according to the HapMap CEU panel⁴.

snpsym	chro	position	ingene	coding	rsquare	conservation	regulation
rs4754298	11	107528494			0.979		
rs6589006	11	107536505	<i>NPAT</i>	intron	0.99		
rs12787445	11	107539334	<i>NPAT</i>	intron	0.952		
rs6589007	11	107545314	<i>NPAT</i>	intron	0.99		
rs2070661	11	107549198	<i>NPAT</i>	exon7*	0.958		
rs11212538	11	107551166	<i>NPAT</i>	intron	0.934		
rs1850730	11	107556322	<i>NPAT</i>	intron	0.99		
rs4623864	11	107556510	<i>NPAT</i>	intron	0.99		
rs4753833	11	107562640	<i>NPAT</i>	intron	0.99		
rs7118967	11	107563066	<i>NPAT</i>	intron	0.957		Yes
rs3781868	11	107564779	<i>NPAT</i>	intron	0.987		
rs2056267	11	107567018	<i>NPAT</i>	intron	0.99		
rs11212546	11	107570145	<i>NPAT</i>	intron	0.99		
rs2083707	11	107571340	<i>NPAT</i>	intron	0.925		
rs1607476	11	107580371	<i>NPAT</i>	intron	0.99		
rs4754305	11	107581122	<i>NPAT</i>	intron	0.99		
rs11605442	11	107583067	<i>NPAT</i>	intron	0.973		
rs11212551	11	107583903	<i>NPAT</i>	intron	0.99		
rs609557	11	107589723	<i>NPAT</i>	intron	0.99		
rs183459	11	107594407	<i>NPAT</i>	intron	0.958		
rs183460	11	107595920	<i>NPAT</i>	intron	0.984		
rs228589	11	107598418	<i>NPAT</i>	intron	0.987		Yes ^s
rs228590	11	107601351	<i>ATM</i>	intron	0.99		
rs228591	11	107602543	<i>ATM</i>	intron	0.987		
rs641605	11	107607129	<i>ATM</i>	intron	1		
rs623860	11	107611992	<i>ATM</i>	intron	0.971		
rs228599	11	107612870	<i>ATM</i>	intron	1		
rs600931	11	107622545	<i>ATM</i>	intron	1		
rs599406	11	107623444	<i>ATM</i>	intron	1		
rs694376	11	107624258	<i>ATM</i>	intron	0.904		
rs599164	11	107625649	<i>ATM</i>	intron	1		
rs228592	11	107628399	<i>ATM</i>	intron	1		
rs672655	11	107634867	<i>ATM</i>	intron	1		
rs627418	11	107636435	<i>ATM</i>	intron	0.971		
rs664677	11	107648392	<i>ATM</i>	intron	0.971		
rs618499	11	107654049	<i>ATM</i>	intron	0.959		

Supplementary Table 6 (continued 1)

snpym	chro	position	ingene	coding	rsquare	conservation	regulation
rs4987982	11	107656479	ATM	intron	1		
rs1003624	11	107657855	ATM	intron	1		
rs624366	11	107659307	ATM	intron	0.997		
rs654005	11	107660607	ATM	intron	1		
rs592955	11	107661683	ATM	intron	0.906		
rs609261	11	107663344	ATM	intron	1		
rs645485	11	107674073	ATM	intron	0.987		
rs619972	11	107674829	ATM	intron	1		
rs599558	11	107682748	ATM	intron	1		
rs660429	11	107686721	ATM	intron	1		
rs673281	11	107687279	ATM	intron	0.965		
rs620613	11	107690688	ATM	intron	1		
rs595747	11	107699283	ATM	intron	0.968		
rs662218	11	107699738	ATM	intron	1		
rs662578	11	107699767	ATM	intron	1		
rs609655	11	107709463	ATM	intron	0.965		
rs227061	11	107710539	ATM	intron	1		
rs227062	11	107710593	ATM	intron	1		
rs227064	11	107712603	ATM	intron	0.965		
rs227068	11	107715319	ATM	intron	1		
rs227070	11	107716622	ATM	intron	0.965		
rs227072	11	107717303	ATM	intron	1		
rs227073	11	107717902	ATM	intron	0.997		
rs227074	11	107720305	ATM	intron	1		
rs172896	11	107722259	ATM	intron	1		
rs227075	11	107723406	ATM	intron	0.959		
rs425538	11	107724549	ATM	intron	0.968		
rs419716	11	107726309	ATM	intron	0.997		
rs374443	11	107726875	ATM	intron	1		
rs227041	11	107728011	ATM	intron	0.997		
rs227040	11	107728601	ATM	intron	0.997		
rs664143	11	107730871	ATM	intron	0.965		
rs652541	11	107731235	ATM	intron	0.962		Yes
rs227053	11	107732065	ATM	intron	1		
rs227092	11	107741993	ATM	3UTR	0.993		
rs4585	11	107744838	ATM	3UTR†	1		
rs652311	11	107745279			1		
rs227087	11	107749324			1		
rs186595	11	107756421			1		
rs573890	11	107756573			0.99		
rs227077	11	107758462			0.997		
rs10789659	11	107761038	C11orf65	intron	1		
rs113995	11	107762047	C11orf65	intron	1		Yes
rs227055	11	107766471	C11orf65	intron	0.965		
rs172894	11	107767300	C11orf65	intron	0.971		
rs227056	11	107767607	C11orf65	intron	0.997		
rs186593	11	107767649	C11orf65	intron	0.959		
rs227058	11	107770423	C11orf65	intron	1		
rs172895	11	107771086	C11orf65	intron	1		
rs7931930	11	107773496	C11orf65	intron	1		
rs9667658	11	107781301	C11orf65	intron	1		

Supplementary Table 6 (continued 2)

snpsym	chro	position	ingene	coding	rsquare	conservation	regulation
rs2356801	11	107787209	<i>C11orf65</i>	intron	1		
rs11212617	11	107788371	<i>C11orf65</i>	intron	1		
rs10890834	11	107791653	<i>C11orf65</i>	intron	1		
rs1583598	11	107811199	<i>C11orf65</i>	intron	0.968		
rs6589019	11	107830171	<i>C11orf65</i>	intron	0.873		
rs4754324	11	107830658	<i>C11orf65</i>	intron	0.965		
rs7942014	11	107831384	<i>C11orf65</i>	intron	0.965		
rs5023001	11	107840748	<i>C11orf65</i>	intron	0.956		
rs3901851	11	107857545	<i>KDELC2</i>	intron	0.949		
rs3765632	11	107858228	<i>KDELC2</i>	intron	0.919		
rs2118309	11	107872663	<i>KDELC2</i>	intron	0.956		

Columns 'ingene' and 'coding' indicate whether a SNP is in the gene transcript and whether it is in the exon, intron or UTR region of the transcript. Column 'conservation' indicates whether a SNP is in genomic region conserved across vertebrate species. Column 'regulation' indicates whether a SNP is in predicted regulatory elements.

*rs2070661 is a non-synonymous SNP in gene *NPAT* however no functional change is predicted according to SIFT, PolyPhen and PANTHER.

§SNP rs228589, which is in intron 1 of the *NPAT* gene, is in a predicted promoter of *ATM*, hence having the potential to affect the transcription of *ATM*^{5,6}.

†Studies have shown that addition of poly A tails to mRNA transcripts requires not only the consensus polyadenylation signal AATAAA, but also sequences located 10 – 30bp downstream, termed the GU-rich element⁷. Deletion of these sequences have a profound effect on the efficiency of polyadenylation⁸. The sequence of the DCE is somewhat variable, but is usually UG rich, and the actual cleavage site is commonly preceded by a CA dinucleotide⁹. Variant rs4585 lies 24bp downstream of an alternative polyadenylation site within the *ATM* transcript. This is within the region that is predicted to contain its DCE. Eight of the nucleotides immediately prior to rs4584 are U or G, and the SNP itself is preceded by a CA dinucleotide. This raises the possibility that rs4585 may influence the polyadenylation dynamics, and thus the stability, of *ATM* transcripts utilising this polyadenylation site.

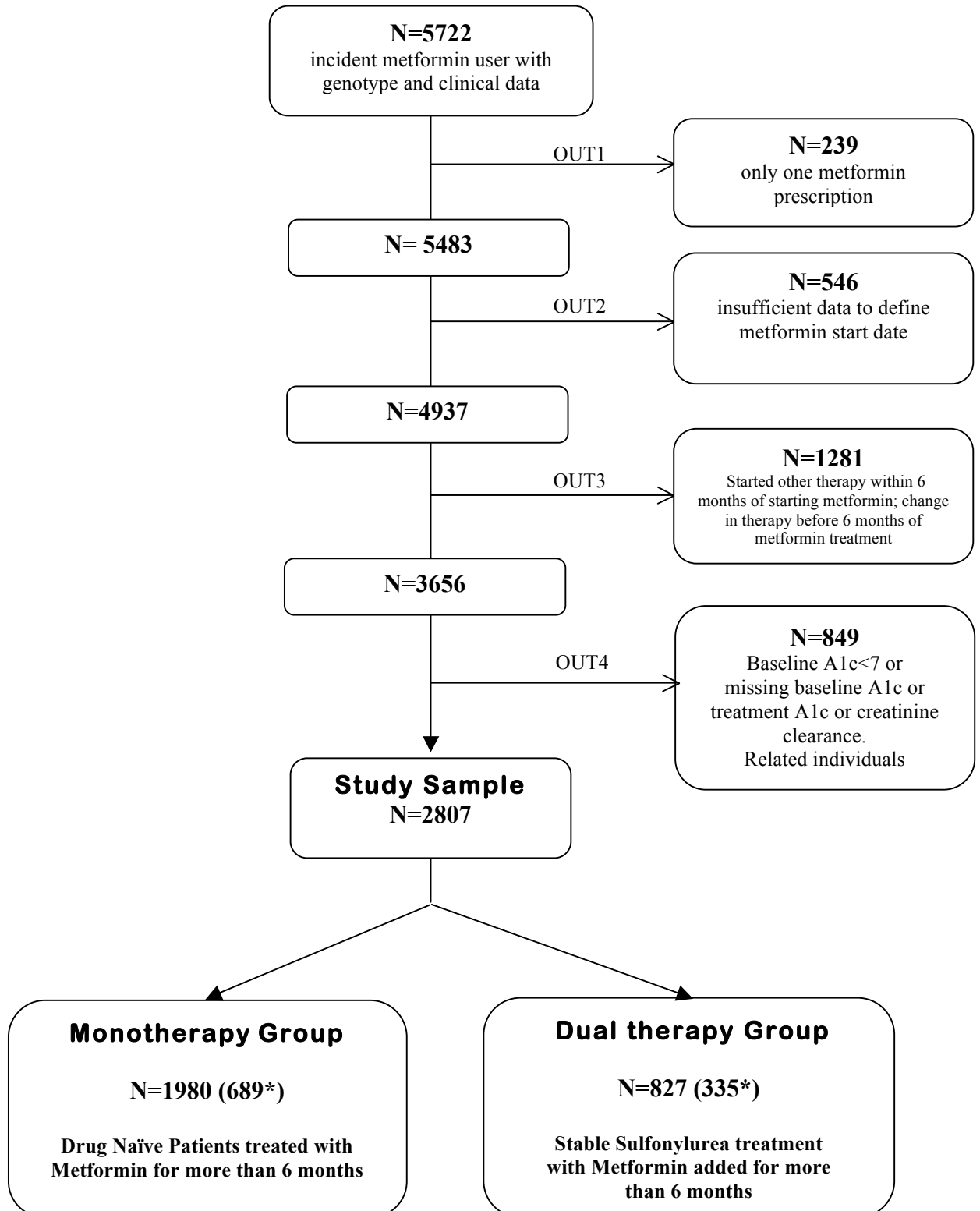
References for supplementary tables

1. Dixon, A.L., *et al.* A genome-wide association study of global gene expression. *Nat Genet* **39**, 1202-1207 (2007).
2. Myers, A.J., *et al.* A survey of genetic human cortical gene expression. *Nat Genet* **39**, 1494-1499 (2007).
3. Schadt, E.E., *et al.* Mapping the genetic architecture of gene expression in human liver. *PLoS Biol* **6**, e107 (2008).
4. McCarroll, S.A., *et al.* Integrated detection and population-genetic analysis of SNPs and copy number variation. *Nat Genet* **40**, 1166-1174 (2008).
5. Trinkle, N.D., Aldred, S.J., Saldanha, A.J. & Myers, R.M. Identification and functional analysis of human transcriptional promoters. *Genome Res* **13**, 308-312 (2003).
6. King, D.C., *et al.* Evaluation of regulatory potential and conservation scores for detecting cis-regulatory modules in aligned mammalian genome sequences. *Genome Res* **15**, 1051-1060 (2005).
7. Colgan, D.F. & Manley, J.L. Mechanism and regulation of mRNA polyadenylation. *Genes Dev* **11**, 2755-2766 (1997).
8. Sadofsky, M. & Alwine, J.C. Sequences on the 3' side of hexanucleotide AAUAAA affect efficiency of cleavage at the polyadenylation site. *Mol Cell Biol* **4**, 1460-1468 (1984).
9. Chen, F., MacDonald, C.C. & Wilusz, J. Cleavage site determinants in the mammalian polyadenylation signal. *Nucleic Acids Res* **23**, 2614-2620 (1995).

SUPPLEMENTARY FIGURES

Supplementary figure 1.

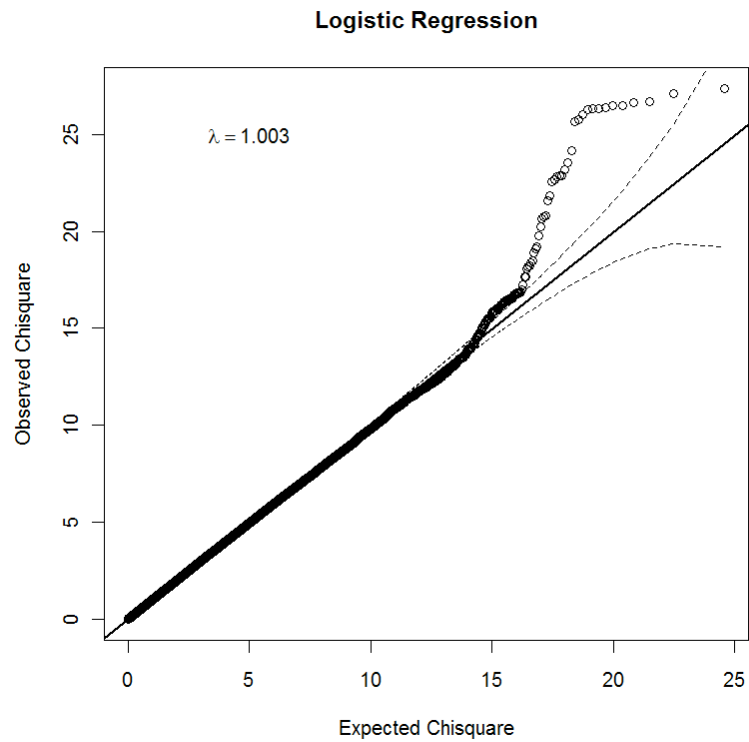
Sample Ascertainment Flow Chart. There was no difference by rs1121617 genotype at each selection/exclusion stage in the definition of the discovery cohort consistent with there being no effect of genotype on metformin tolerability



* number of patients in GWA

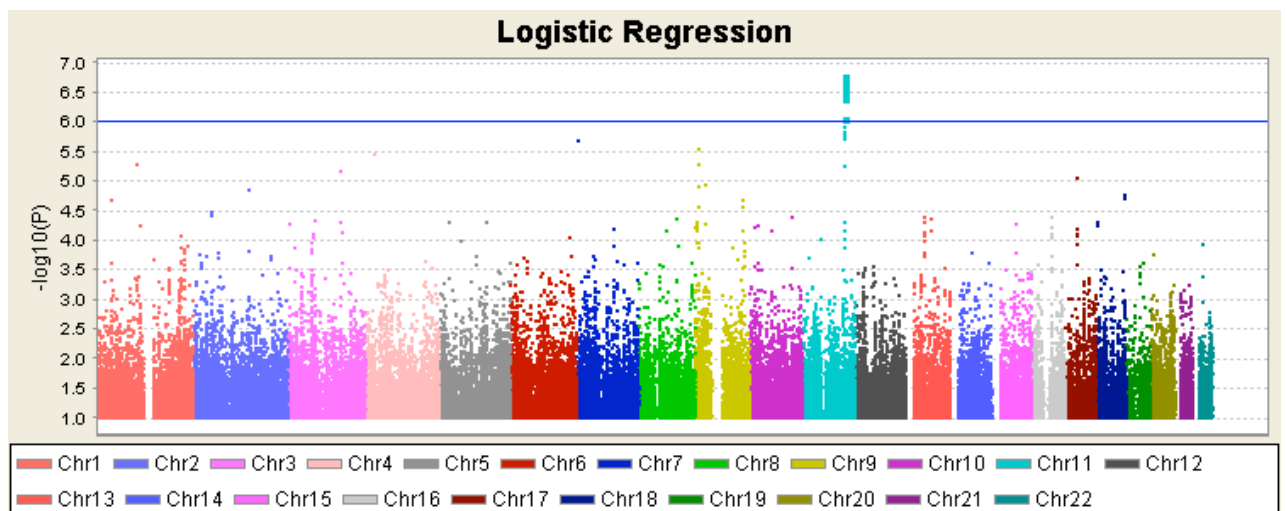
Supplementary Figure 2

Quantile-Quantile plots. The genomic control "inflation factor" $\lambda=1.003$ for logistic regression. The dashed lines are 95% confidence interval



Supplementary Figure 3

Manhattan plot of single marker association test in the 1024 GoDARTS patients



SUPPLEMENTARY NOTES

Sample Ascertainment and Covariates

Inclusion criteria. As shown in the supplementary Figure 1, patients had to fulfill the following criteria to be included in the current study:

1. A pre-treatment HbA1c must be measured within 6 months prior to starting metformin and must be greater than 7% and less than 14%.
2. No new treatment should be started or stopped within 6 months prior to or after metformin start
3. Metformin treatment should continue for at least 6 months
4. At least one HbA1c measurement must be recorded whilst on metformin and within 18 months of commencing metformin.

Covariates. Age, sex and weight were used to derive the creatinine clearance so were not included separately in the models. The covariates that were used in both the logistic and linear regression analyses were defined as follows:

- 1) **Baseline HbA1c**: The baseline HbA1c value closest to starting metformin, and within the time period six months before and seven days after starting metformin.
- 2) **Baseline Gap**: The number of days between the baseline HbA1c and start of metformin was used to account for the unobserved deterioration of glycaemia between the HbA1c measure and initiation of metformin
- 3) **Drug Adherence**: Adherence was estimated as
$$\text{Adherence} = \text{sum (days covered by each prescription)} / \text{days in the study period}$$
in which the days covered by a prescription was calculated by dividing the dispensing quantity by daily dose; if one prescription covered a time period beyond next prescription start, the extra days were not taken over to the calculation for next prescription.
- 4) **Daily Dose**: The average daily dose during the 3 months prior to the minimum HbA1c was achieved
- 5) **Creatinine Clearance**: The creatinine clearance rate was calculated using the Cockcroft-Gault equation as
$$\text{GFR} = (140 - \text{age}) * (\text{weight in kg}) * (0.85 \text{ if female}) / (72 * \text{creatinine in mg/dL})$$

in which weight and serum creatinine concentration were the average of measurements from two years either side of the index date; age was at index date.

General Model. The general Metformin drug response outcome model was:

$$\text{outcome} \sim \text{baseline HbA1c} + \text{adherence} + \text{daily dose} + \text{Creatinine Clearance} + \text{baseline gap} + \text{treatment group} + \text{genotype}$$

GWAS Genotyping and Quality Control

DNA samples. Genomic DNA for all cases was shipped to the Sanger Institute, Cambridge. Where there was sufficient DNA, quality was validated using the Sequenom iPLEX assay designed to genotype four gender SNPs and 26 SNPs present on the Illumina Beadchips. DNA concentrations were quantified using a PicoGreen assay (Invitrogen) and an aliquot assayed by agarose gel electrophoresis. A DNA sample was considered to pass quality control if the DNA concentration was greater than or equal to 50 ng/ μ l, the DNA was not degraded, the gender assignment from the iPLEX assay matched that provided in the patient data manifest and genotypes were obtained for at least two thirds of the SNPs on the iPLEX.

Genotyping. Samples were genotyped at Affymetrix's service laboratory on the Genome-Wide Human SNP Array 6.0. For all samples passing Affymetrix's laboratory quality control, raw intensities were renormalized within collections using CelQuantileNorm. These normalized intensities were used to call genotypes with an updated version of the Chiamo software adapted for Affymetrix 6.0 SNP data.

By Individual QC. Genotype data quality control was via the protocol that was established for the WTCCC2 studies¹. A few refinements to the conventional fixed-threshold based quality control have been made to obtain the more powerful sets of samples and SNPs for subsequent GWA analysis. For all individuals, we explicitly modelled the data as a mixture of 'normal' and 'outlier' individuals for each of ancestry, missing data and heterozygosity, and sex assignment. We fitted each model in a Bayesian framework and excluded individuals whose posterior probability of belonging to the outlier class was above 0.5. This approach replaces the traditional concept of fixed exclusion thresholds for parameters such as call rate, heterozygosity and ancestry.

Relatedness. To assess relatedness among study individuals, we compared each individual with the 100 individuals they were most closely related to (on the basis of genome-wide levels of allele sharing) and used a hidden Markov model (HMM) to decide, at each position in their genome, whether the two individuals shared 0, 1 or 2 chromosomes identical by descent (IBD). This allowed a more refined assessment of the relatedness between individuals than genome-wide sharing statistics (for example, parent-child relationships can be distinguished from those of siblings). Individuals were removed from the study iteratively to ensure there was no pair of individuals with $IBD \geq 5\%$. Within each pair of putatively related individuals, the individual with more missing genotypes was removed.

By SNP QC. For each SNP, we considered a measure of the (Fisher) information carried by the genotype calls for the underlying allele frequency. This will decrease as the number of individuals with low posterior probabilities for the most likely call increases, and it can be considered a more refined measure of both missing data and minor allele frequency. The measure is calculated automatically by the program SNPtest. SNPs were removed if this information measure was below 0.98 or if the estimated minor allele frequency was below 0.01%. SNPs that significantly deviated from Hardy Weinberg Equilibrium ($p < 1 \times 10^{-6}$) were also removed and the final data set consisted of 705,125 autosomal SNPs.

Concordance. Part of the current GWA sample was used as replication cohort in the WTCCC1 T2D case control study². The overlapping genotyping is on a maximum number of 116 SNPs by 1779 individuals, depending on whether the SNP was taken into the second stage of the WTCCC1 replication. A total number of 457 discrepancies out of 163391 informative comparisons were observed, which gives a concordance rate of 99.73% between the two studies. Individuals with more than 10% discordance were removed from the current study.

rs11212617 Association with Quantitative Glycaemic Traits.

We requested unpublished summary statistics for the top SNPs of interest from meta-analyses of GWAS datasets, conducted by the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) to identify genetic determinants of quantitative glycaemic traits in non-diabetic individuals. The published fasting trait meta-analysis included 20 cohorts with available fasting glucose and insulin

measurements and GWAS data, for a total of 35,914-38,237 individuals (depending on the SNP and the trait); participating cohorts are listed in the online supplement to ref 3. The unpublished HbA_{1c} meta-analysis includes 23 cohorts with available HbA_{1c} measurements and GWAS data, for a total of 36,099 subjects (35,841 with valid genotypes for these SNPs). For the latter, cohorts include: B58C-WTCCC (n=1,428), BLSA (n=490), DGI (n=480), EPIC cancer cases (n=957), EPIC cohort (n=1,911), Fenland (n=1,378), Framingham (n=1,996), KORA F3 (n=1,644), Lollipop (n=770), SardiNIA (n=3,346), 1958BC-T1DGC (n=2,501), ARIC (n=6,777), Croatia (n=659), deCODE (n=342), DESIR (n=731), GenomeEUtwin (n=568), HEALTH2000 (n=1,205), KORA_S4 (n=1,814), NTRNESDA (n=1,452), ORCADES (n=651), PROCARDIS (n=831), SHIP (n=3,538) and Sorbs (n=630). All participants were non-diabetic adults of European ancestry from Europe or the United States. Local research ethics committees approved all studies and all participants gave informed consent. In each study HbA_{1c} was measured from whole blood with NGSP-certified methods; details on insulin measurement are listed in the supplementary material to ref.³¹. SNPs were either directly genotyped or imputed from the HapMap CEU phase 2 reference panel using the software programs MACH or IMPUTE. QC metrics were applied to genotyped (Hardy-Weinberg equilibrium $P < 10^{-4}$ or 10^{-6} and call-rate < 0.90 or 0.95) and imputed (observed-by-expected variance ratio [r2.hat] < 0.3 in MACH, or proper-info < 0.4 in IMPUTE) SNPs. In each cohort, a linear regression model was fitted using natural log transformed fasting insulin or HOMA-IR, or untransformed HbA_{1c} as the dependent variable to evaluate the additive effect of genotyped and imputed SNPs, adjusting for age, sex, study-site (when applicable) and family structure if present. Regression estimates for each SNP were combined across studies in each meta-analysis using a fixed effect inverse-variance approach, as implemented in the METAL software.

Reference to Supplementary Notes

1. Barrett, J.C., *et al.* Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. *Nat Genet* **41**, 1330-1334 (2009).
2. Zeggini, E., *et al.* Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* **316**, 1336-1341 (2007).
3. Dupuis, J., *et al.* New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* **42**, 105-116 (2010).

Consortia Membership

Membership of Wellcome Trust Case Control Consortium 2

Management Committee

Peter Donnelly (Chair)^{1,2}, Leena Peltonen (Deputy Chair)³, Jenefer M Blackwell^{4,5}, Elvira Bramon⁶, Matthew A Brown⁷, Juan P Casas⁸, Aiden Corvin⁹, Nicholas Craddock¹⁰, Panos Deloukas³, Audrey Duncanson¹¹, Janusz Jankowski¹², Hugh S Markus¹³, Christopher G Mathew¹⁴, Mark I McCarthy¹⁵, Colin NA Palmer¹⁶, Robert Plomin¹⁷, Anna Rautanen¹, Stephen J Sawcer¹⁸, Nilesh J Samani¹⁹, Richard C Trembath¹⁴, Ananth C Viswanathan²⁰, Nicholas W Wood²¹

Data and Analysis Group

Chris C A Spencer¹, Gavin Band¹, Céline Bellenguez¹, Colin Freeman¹, Garrett Hellenthal¹, Eleni Giannoulatou¹, Matti Pirinen¹, Richard Pearson¹, Amy Strange¹, Zhan Su¹, Damjan Vukcevic¹, Peter Donnelly^{1,2}

DNA, Genotyping, Data QC and Informatics Group

Cordelia Langford³, Sarah E Hunt³, Sarah Edkins³, Rhian Gwilliam³, Hannah Blackburn³, Suzannah J Bumpstead³, Serge Dronov³, Matthew Gillman³, Emma Gray³, Naomi Hammond³, Alagurevathi Jayakumar³, Owen T McCann³, Jennifer Liddle³, Marc L Perez³, Simon C Potter³, Radhi Ravindrarajah³, Michelle Ricketts³, Matthew Waller³, Paul Weston³, Sara Widaa³, Pamela Whittaker³, Panos Deloukas³, Leena Peltonen³

Publications Committee

Christopher G Mathew (Chair)¹⁴, Jenefer M Blackwell^{4,5}, Matthew A Brown⁷, Aiden Corvin⁹, Mark I McCarthy¹⁵, Chris C A Spencer¹

1 Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7LJ, UK; 2 Dept Statistics, University of Oxford, Oxford OX1 3TG, UK; 3 Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; 4 Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, 100 Roberts Road, Subiaco, Western Australia 6008; 5 Cambridge Institute for Medical Research, University of Cambridge School of Clinical Medicine, Cambridge CB2 0XY, UK; 6 Department of Psychosis Studies, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King's College London and The South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AF, UK; 7 Diamantina Institute of Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Brisbane, Queensland, Australia; 8 Dept Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT and Dept Epidemiology and Public Health, University College London WC1E 6BT, UK; 9 Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine, Trinity College Dublin, Dublin 2, Eire; 10 Dept Psychological Medicine, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN, UK; 11 Molecular and Physiological Sciences, The Wellcome Trust, London NW1 2BE; 12

Centre for Digestive Diseases, Queen Mary University of London, London E1 2AD, UK and Digestive Diseases Centre, Leicester Royal Infirmary, Leicester LE7 7HH, UK and Department of Clinical Pharmacology, Old Road Campus, University of Oxford, Oxford OX3 7DQ, UK; 13 Clinical Neurosciences, St George's University of London, London SW17 0RE; 14 King's College London Dept Medical and Molecular Genetics, School of Medicine, Guy's Hospital, London SE1 9RT, UK; 15 Oxford Centre for Diabetes, Endocrinology and Metabolism (ICDEM), Churchill Hospital, Oxford OX3 7LJ, UK; 16 Biomedical Research Centre, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; 17 King's College London Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Denmark Hill, London SE5 8AF, UK; 18 University of Cambridge Dept Clinical Neurosciences, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK; 19 Dept Cardiovascular Science, University of Leicester, Glenfield Hospital, Leicester LE3 9QP; 20 NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London EC1V 2PD, UK; 21 Dept Molecular Neuroscience, Institute of Neurology, Queen Square, London WC1N 3BG, UK.

† Additional Acknowledgement. ACV acknowledges (a proportion of their) financial support from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health

MAGIC Investigators

Josée Dupuis^{1,2,177}, Claudia Langenberg^{3,177}, Inga Prokopenko^{4,5,177}, Richa Saxena^{6,7,177}, Nicole Soranzo^{8,9,177}, Anne U Jackson¹⁰, Eleanor Wheeler¹¹, Nicole L Glazer¹², Nabila Bouatia-Naji¹³, Anna L Gloyn⁴, Cecilia M Lindgren^{4,5}, Reedik Mägi^{4,5}, Andrew P Morris⁵, Joshua Randall⁵, Toby Johnson^{14–16}, Paul Elliott^{17,176}, Denis Rybin¹⁸, Gudmar Thorleifsson¹⁹, Valgerdur Steinthorsdottir¹⁹, Peter Henneman²⁰, Harald Grallert²¹, Abbas Dehghan²², Jouke Jan Hottenga²³, Christopher S Franklin²⁴, Pau Navarro²⁵, Kijoung Song²⁶, Anuj Goel^{5,27}, John R B Perry²⁸, Josephine M Egan²⁹, Taina Lajunen³⁰, Niels Grarup³¹, Thomas Sparsø³¹, Alex Doney³², Benjamin F Voight^{6,7}, Heather M Stringham¹⁰, Man Li³³, Stavroula Kanoni³⁴, Peter Shrader³⁵, Christine Cavalcanti-Proença¹³, Meena Kumari³⁶, Lu Qi³⁷, Nicholas J Timpson³⁸, Christian Gieger²¹, Carina Zabena³⁹, Ghislain Rocheleau^{40,41}, Erik Ingelsson^{42,43}, Ping An⁴⁴, Jeffrey O'Connell⁴⁵, Jian'an Luan³, Amanda Elliott^{6,7}, Steven A McCarroll^{6,7}, Felicity Payne¹¹, Rosa Maria Roccascocca¹¹, François Pattou⁴⁶, Praveen Sethupathy⁴⁷, Kristin Ardlie⁴⁸, Yavuz Ariyurek⁴⁹, Beverley Balkau⁵⁰, Philip Barter⁵¹, John P Beilby^{52,53}, Yoav Ben-Shlomo⁵⁴, Rafn Benediktsson^{55,56}, Amanda J Bennett⁴, Sven Bergmann^{14,16}, Murielle Bochud¹⁵, Eric Boerwinkle⁵⁷, Amélie Bonnefond¹³, Lori L Bonnycastle⁴⁷, Knut Borch-Johnsen^{58,59}, Yvonne Böttcher⁶⁰, Eric Brunner³⁶, Suzannah J Bumpstead⁸, Guillaume Charpentier⁶¹, Yii-Der Ida Chen⁶², Peter Chines⁴⁷, Robert Clarke⁶³, Lachlan J McCoin¹⁷, Matthew N Cooper⁶⁴, Marilyn Cornelis³⁷, Gabe Crawford⁶, Laura Crisponi⁶⁵, Ian N M Day³⁸, Eco J Cde Geus²³, Jerome Delplanque¹³, Christian Dina¹³, Michael R Erdos⁴⁷, Annette C Fedson^{64,66}, Antje Fischer-Rosinsky^{67,68}, Nita G Frouhi³, Caroline S Fox^{2,69}, Rune Frants⁷⁰, Maria Grazia Franzosi⁷¹, Pilar Galan⁷², Mark O Goodarzi⁶², Jürgen Graessler⁷³, Christopher J Groves⁴, Scott Grundy⁷⁴, Rhian Gwilliam⁸, Ulf Gyllenstein⁷⁵, Samy Hadjadj⁷⁶, Göran Hallmans⁷⁷, Naomi Hammond⁸, Xijing Han¹⁰, Anna-Liisa Hartikainen⁷⁸, Neelam Hassanali⁴, Caroline Hayward²⁵, Simon C Heath⁷⁹, Serge Hercberg⁸⁰, Christian Herder⁸¹, Andrew A Hicks⁸², David R Hillman^{66,83}, Aroon D Hingorani³⁶, Albert Hofman²², Jennie Hul^{52,84}, Joe Hung^{85,86}, Bo Isomaa^{87,88}, Paul R V Johnson^{4,89}, Torben Jørgensen^{90,91}, Antti Jula⁹², Marika Kaakinen⁹³, Jaakko Kaprio^{94–96}, Y Antero Kesaniemi⁹⁷, Mika Kivimäki³⁶, Beatrice Knight⁹⁸, Seppo Koskinen⁹⁹, Peter Kovacs¹⁰⁰, Kirsten Ohm Kyvik¹⁰¹, G Mark Lathrop⁷⁹, Debbie A Lawlor³⁸, Olivier Le Bacquer¹³, Cécile Lecoeur¹³, Yun Li¹⁰, Valeriya Lyssenko¹⁰², Robert Mahley¹⁰³, Massimo Mangino⁹, Alisa K Manning¹, María Teresa Martínez-Larrad³⁹, Jarred B McAteer^{6,104,105}, Laura J McCulloch⁴, Ruth McPherson¹⁰⁶, Christa Meisinger²¹, David Melzer²⁸, David Meyre¹³, Braxton DMitchell⁴⁵, Mario A Morken⁴⁷, Sutapa Mukherjee^{66,83}, Silvia Naitza⁶⁵, Narisu Narisu⁴⁷, Matthew J Neville^{4,107}, Ben A Oostra¹⁰⁸, Marco Orrù⁶⁵, Ruth Pakyz⁴⁵, Colin N A Palmer¹⁰⁹, Giuseppe Paolisso¹¹⁰, Cristian Pattaro⁸², Daniel Pearson⁴⁷, John F Peden^{5,27}, Nancy L Pedersen⁴², Markus Perola^{96,111,112}, Andreas F H Pfeiffer^{67,68}, Irene Pichler⁸², Ozren Polasek¹¹³, Danielle Posthuma^{23,114}, Simon C Potter⁸, Anneli Pouta¹¹⁵, Michael A Province⁴⁴, Bruce M Psaty^{116,117}, Wolfgang Rathmann¹¹⁸, Nigel W Rayner^{4,5}, Kenneth Rice¹¹⁹, Samuli Ripatti^{96,111}, Fernando Rivadeneira^{22,120}, Michael Roden^{81,121}, Olov Rolandsson¹²², Anneli Sandbaek¹²³, Manjinder Sandhu^{3,124}, Serena Sanna⁶⁵, Avan Aihie Sayer¹²⁵, Paul Scheet¹²⁶, Laura J Scott¹⁰, Udo Seedorf¹²⁷, Stephen J Sharp³, Beverley Shields⁹⁸, Gunnar Sigurðsson^{55,56}, Eric J G Sijbrands^{22,120}, Angela Silveira¹²⁸, Laila Simpson^{64,66}, Andrew Singleton¹²⁹, Nicholas L Smith^{130,131}, Ulla Sovio¹⁷, Amy Swift⁴⁷, Holly Syddall¹²⁵, Ann-Christine Syvänen¹³², Toshiko Tanaka^{133,134}, Barbara Thorand²¹, Jean Tichet¹³⁵, Anke Tönjes^{60,136}, Tiinamaija Tuomi^{87,137}, André G Uitterlinden^{22,120}, Ko Willems van Dijk^{70,138}, Mandy van Hoek¹²⁰, Dhiraj Varma⁸, Sophie Visvikis-Siest¹³⁹, Veronique Vitart²⁵, Nicole Vogelzangs¹⁴⁰, Gérard Waeber¹⁴¹, Peter J Wagner^{96,111}, Andrew Walley¹⁴², G Bragi Walters¹⁹, Kim L Ward^{64,66}, Hugh Watkins^{5,27}, Michael N Weedon²⁸, Sarah H Wild²⁴, Gonneke Willemsen²³, Jaqueline C M Witteman²², John W G Yarnell¹⁴³, Eleftheria Zeggini^{5,8}, Diana Zelenika⁷⁹, Björn Zethelius^{43,144}, Guangju

Zhai⁹, Jing Hua Zhao³, MCarola Zillikens¹²⁰, DIAGRAM Consortium¹⁴⁵, GIANT Consortium¹⁴⁵, Global BPgen Consortium¹⁴⁵, Ingrid B Borecki⁴⁴, Ruth J F Loos³, Pierre Meneton⁸⁰, Patrik K E Magnusson⁴², David M Nathan^{104,105}, Gordon H Williams^{69,105}, Andrew T Hattersley⁹⁸, Kaisa Silander^{96,111}, Veikko Salomaa¹⁴⁶, George Davey Smith³⁸, Stefan R Bornstein⁷³, Peter Schwarz⁷³, Joachim Spranger^{67,68}, Fredrik Karpe^{4,107}, Alan R Shuldiner⁴⁵, Cyrus Cooper¹²⁵, George V Dedoussis³⁴, Manuel Serrano-Rios³⁹, Andrew D Morris¹⁰⁹, Lars Lind¹³², Lyle J Palmer^{64,66,84}, Frank B Hu^{47,148}, Paul W Franks¹⁴⁹, Shah Ebrahim¹⁵⁰, Michael Marmot³⁶, W H Linda Kao^{33,151,152}, James S Pankow¹⁵³, Michael J Sampson¹⁵⁴, Johanna Kuusisto¹⁵⁵, Markku Laakso¹⁵⁵, Torben Hansen^{31,156}, Oluf Pedersen^{31,59,157}, Peter Paul Pramstaller^{82,158,159}, H Erich Wichmann^{21,160,161}, Thomas Illig²¹, Igor Rudan^{24,162,163}, Alan F Wright²⁵, Michael Stumvoll⁶⁰, Harry Campbell²⁴, James F Wilson²⁴, Anders Hamsten on behalf of Procardis Consortium¹²⁸, Richard N Bergman¹⁶⁴, Thomas A Buchanan^{164,165}, Francis S Collins⁴⁷, Karen L Mohlke¹⁶⁶, Jaakko Tuomilehto^{94,167,168}, Timo T Valle¹⁶⁷, David Altshuler^{6,7,104,105}, Jerome I Rotter⁶², David Siscovick¹⁶⁹, Brenda W J H Penninx¹⁴⁰, Dorret I Boomsma²³, Panos Deloukas⁸, Timothy D Spector^{8,9}, Timothy M Frayling²⁸, Luigi Ferrucci¹⁷⁰, Augustine Kong¹⁹, Unnur Thorsteinsdottir^{19,171}, Kari Stefansson^{19,171}, Cornelia Mvan Duijn²², Yurii S Aulchenko²², Antonio Cao⁶⁵, Angelo Scuteri^{172,177}, David Schlessinger⁴⁷, Manuela Uda⁶⁵, Aimo Ruukonen¹⁷³, Marjo-Riitta Jarvelin^{17,93,174}, Dawn M Waterworth²⁶, Peter Vollenweider¹⁴¹, Leena Peltonen^{8,48,96,111,112}, Vincent Moser²⁶, Goncalo R Abecasis¹⁰, Nicholas J Wareham³, Robert Sladek^{40,41}, Philippe Froguel^{13,142}, Richard M Watanabe^{164,175}, James B Meigs^{35,105}, Leif Groop¹⁰², Michael Boehnke¹⁰, Mark I McCarthy^{4,5,107}, Jose CFlorez^{6,7,104,105} & Inês Barroso¹¹ for the MAGIC investigators

¹Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA. ²National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA. ³Medical Research Council (MRC), Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK. ⁴Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK. ⁵Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. ⁶Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA. ⁷Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA. ⁸Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK. ⁹Twin Research and Genetic Epidemiology Department, King's College London, St Thomas' Hospital Campus, London, UK. ¹⁰Center for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan, USA. ¹¹Metabolic Disease Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK. ¹²Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington, USA. ¹³Centre National de la Recherche Scientifique—Unité Mixte de Recherche 8090, Pasteur Institute, Lille 2—Droit et Santé University, Lille, France. ¹⁴Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland. ¹⁵University Institute of Social and Preventative Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland. ¹⁶Swiss Institute of Bioinformatics, Lausanne, Switzerland. ¹⁷Department of Epidemiology and Public Health, Imperial College London, Faculty of Medicine, Norfolk Place, London, UK. ¹⁸Boston University Data Coordinating Center, Boston, Massachusetts, USA. ¹⁹deCODE Genetics, Reykjavik, Iceland. ²⁰Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands. ²¹Institute of Epidemiology, Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Neuherberg, Germany. ²²Department of Epidemiology, Erasmus Medical College, Rotterdam, The Netherlands. ²³Department of Biological

Psychology, VU University Amsterdam, Amsterdam, The Netherlands. ²⁴Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK. ²⁵MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh, UK. ²⁶Division of Genetics, Research and Development, GlaxoSmithKline, King of Prussia, Pennsylvania, USA. ²⁷Department of Cardiovascular Medicine, University of Oxford, Oxford, UK. ²⁸Genetics of Complex Traits, Institute of Biomedical and Clinical Sciences, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK. ²⁹National Institute of Aging, Baltimore, Maryland, USA. ³⁰Unit for Child and Adolescent Health and Welfare, National Institute for Health and Welfare, Biocenter Oulu, University of Oulu, Oulu, Finland. ³¹Hagedorn Research Institute, Gentofte, Denmark. ³²Department of Medicine and Therapeutics, Level 7, Ninewells Hospital and Medical School, Dundee, UK. ³³Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA. ³⁴Department of Nutrition–Dietetics, Harokopio University, Athens, Greece. ³⁵General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, USA. ³⁶Department of Epidemiology and Public Health, University College London, London, UK. ³⁷Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA. ³⁸MRC Centre for Causal Analyses in Translational Epidemiology, University of Bristol, Bristol, UK. ³⁹Fundación para la Investigación Biomédica del Hospital Clínico San Carlos, Madrid, Spain. ⁴⁰Departments of Medicine and Human Genetics, McGill University, Montreal, Canada. ⁴¹Genome Quebec Innovation Centre, Montreal, Canada. ⁴²Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ⁴³Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden. ⁴⁴Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St. Louis, Missouri, USA. ⁴⁵Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, Maryland, USA. ⁴⁶INSERM U859, Université de Lille-Nord de France, Lille, France. ⁴⁷Genome Technology Branch, National Human Genome Research Institute, Bethesda, Maryland, USA. ⁴⁸The Broad Institute, Cambridge, Massachusetts, USA. ⁴⁹Leiden Genome Technology Center, Leiden University Medical Center, Leiden, The Netherlands. ⁵⁰INSERM U780, Paris Sud University, Villejuif, France. ⁵¹The Heart Research Institute, Sydney, New South Wales, Australia. ⁵²PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, Nedlands West Australia, Australia. ⁵³School of Surgery and Pathology, University of Western Australia, Nedlands West Australia, Australia. ⁵⁴Department of Social Medicine, University of Bristol, Bristol, UK. ⁵⁵Landspítali University Hospital, Reykjavik, Iceland. ⁵⁶Icelandic Heart Association, Kopavogur, Iceland. ⁵⁷The Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas, USA. ⁵⁸Steno Diabetes Center, Gentofte, Denmark. ⁵⁹Faculty of Health Science, University of Aarhus, Aarhus, Denmark. ⁶⁰Department of Medicine, University of Leipzig, Leipzig, Germany. ⁶¹Endocrinology–Diabetology Unit, Corbeil-Essonnes Hospital, Essonnes, France. ⁶²Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA. ⁶³Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK. ⁶⁴Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Perth, Australia. ⁶⁵Istituto di Neurogenetica e Neurofarmacologia (INN), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Monserrato, Cagliari, Italy. ⁶⁶Western Australian Sleep Disorders Research Institute, Queen Elizabeth Medical Centre II, Perth, Australia. ⁶⁷Department of Endocrinology, Diabetes and Nutrition, Charité-Universitätsmedizin Berlin, Berlin, Germany. ⁶⁸Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany. ⁶⁹Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. ⁷⁰Department of Human Genetics, Leiden University Medical Centre, Leiden, The

Netherlands. ⁷¹Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy. ⁷²Institut National de la Santé et de la Recherche Médicale, Institut National de la Recherche Agronomique, Université Paris 13, Bobigny Cedex, France. ⁷³Department of Medicine III, Division Prevention and Care of Diabetes, University of Dresden, Dresden, Germany. ⁷⁴Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas, USA. ⁷⁵Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden. ⁷⁶Centre Hospitalier Universitaire, de Poitiers, Endocrinologie Diabetologie, CIC INSERM 0802, INSERM U927, Université de Poitiers, Unité de Formation et de Recherche, Médecine Pharmacie, Poitiers, France. ⁷⁷Department of Public Health and Clinical Medicine, Section for Nutritional Research, Umeå University, Umeå, Sweden. ⁷⁸Department of Clinical Sciences, Obstetrics and Gynecology, University of Oulu, University of Oulu, Finland. ⁷⁹Centre National de Génotypage/Institut de génomique/Commissariat à l'énergie atomique, Evry Cedex, France. ⁸⁰INSERM U872, Faculté de Médecine Paris Descartes, Paris Cedex, France. ⁸¹Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany. ⁸²Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso, Bolzano, Italy, Affiliated Institute of the University Lübeck, Lübeck, Germany. ⁸³Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Perth, Australia. ⁸⁴Busselton Population Medical Research Foundation, Sir Charles Gairdner Hospital, Perth, Australia. ⁸⁵Heart Institute of Western Australia, Sir Charles Gairdner Hospital, Nedlands West Australia, Australia. ⁸⁶School of Medicine and Pharmacology, University of Western Australia, Nedlands West Australia, Australia. ⁸⁷Folkhalsan Research Centre, Helsinki, Finland. ⁸⁸Malmska Municipal Health Care Center and Hospital, Jakobstad, Finland. ⁸⁹Nuffield Department of Surgery, University of Oxford, Oxford, UK. ⁹⁰Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark. ⁹¹Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark. ⁹²National Institute for Health and Welfare, Unit of Population Studies, Turku, Finland. ⁹³Institute of Health Sciences and Biocenter Oulu, University of Oulu, Oulu, Finland. ⁹⁴Department of Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland. ⁹⁵National Institute for Health and Welfare, Unit for Child and Adolescent Mental Health, Helsinki, Finland. ⁹⁶Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. ⁹⁷Department of Internal Medicine and Biocenter Oulu, Oulu, Finland. ⁹⁸Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK. ⁹⁹National Institute for Health and Welfare, Unit of Living Conditions, Health and Wellbeing, Helsinki, Finland. ¹⁰⁰Interdisciplinary Centre for Clinical Research, University of Leipzig, Leipzig, Germany. ¹⁰¹The Danish Twin Registry, Epidemiology, Institute of Public Health, University of Southern Denmark, Odense, Denmark. ¹⁰²Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, University Hospital Malmö, Malmö, Sweden. ¹⁰³Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, California, USA. ¹⁰⁴Diabetes Research Center, Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹⁰⁵Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. ¹⁰⁶Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada. ¹⁰⁷Oxford National Institute for Health Research, Biomedical Research Centre, Churchill Hospital, Oxford, UK. ¹⁰⁸Department of Clinical Genetics, Erasmus Medical College, Rotterdam, The Netherlands. ¹⁰⁹Biomedical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. ¹¹⁰Department of Geriatric Medicine and Metabolic Disease, Second University of Naples, Naples, Italy. ¹¹¹National Institute for Health and Welfare, Unit of Public Health Genomics, Helsinki, Finland. ¹¹²Department of Medical Genetics, University of Helsinki, Helsinki, Finland. ¹¹³Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija

Stampar School of Public Health, Medical School, University of Zagreb, Rockefellerova, Zagreb, Croatia. ¹¹⁴Department of Clinical Genetics, VU University and Medical Center, Amsterdam, The Netherlands. ¹¹⁵Department of Obstetrics and Gynaecology, Oulu University Hospital, Oulu, Finland. ¹¹⁶Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, Washington, USA. ¹¹⁷Group Health Research Institute, Group Health Cooperative, Seattle, Washington, USA. ¹¹⁸Institute of Biometrics and Epidemiology, German Diabetes Centre, Leibniz Centre at Heinrich Heine University Düsseldorf, Düsseldorf, Germany. ¹¹⁹Department of Biostatistics, University of Washington, Seattle, Washington, USA. ¹²⁰Department of Internal Medicine, Erasmus Medical College, Rotterdam, The Netherlands. ¹²¹Department of Metabolic Diseases, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. ¹²²Department of Public Health and Clinical Medicine, Section for Family Medicine, Umeå University, Umeå, Sweden. ¹²³School of Public Health, Department of General Practice, University of Aarhus, Aarhus, Denmark. ¹²⁴Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK. ¹²⁵MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, UK. ¹²⁶Department of Epidemiology, University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA. ¹²⁷Leibniz-Institut für Arterioskleroseforschung an der Universität Münster, Münster, Germany. ¹²⁸Atherosclerosis Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden. ¹²⁹Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland, USA. ¹³⁰Department of Epidemiology, University of Washington, Seattle, Washington, USA. ¹³¹Seattle Epidemiologic Research and Information Center, Department of Veterans Affairs Office of Research and Development, Seattle, Washington, USA. ¹³²Department of Medical Sciences, Uppsala University, Uppsala, Sweden. ¹³³Medstar Research Institute, Baltimore, Maryland, USA. ¹³⁴Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, USA. ¹³⁵Institut interrégional pour la santé (IRSA), La Riche, France. ¹³⁶Coordination Centre for Clinical Trials, University of Leipzig, Leipzig, Germany. ¹³⁷Department of Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. ¹³⁸Department of Internal Medicine, Leiden University Medical Centre, Leiden, The Netherlands. ¹³⁹Research Unit, Cardiovascular Genetics, Nancy University Henri Poincaré, Nancy, France. ¹⁴⁰EMGO Institute for Health and Care Research, Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. ¹⁴¹Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. ¹⁴²Genomic Medicine, Imperial College London, Hammersmith Hospital, London, UK. ¹⁴³Epidemiology and Public Health, Queen's University Belfast, Belfast, UK. ¹⁴⁴Medical Products Agency, Uppsala, Sweden. ¹⁴⁵See Supplementary Note for a full list of authors. ¹⁴⁶National Institute for Health and Welfare, Unit of Chronic Disease Epidemiology and Prevention, Helsinki, Finland. ¹⁴⁷Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA. ¹⁴⁸Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA. ¹⁴⁹Genetic Epidemiology and Clinical Research Group, Department of Public Health and Clinical Medicine, Section for Medicine, Umeå University Hospital, Umeå, Sweden. ¹⁵⁰London School of Hygiene and Tropical Medicine, London, UK. ¹⁵¹Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA. ¹⁵²The Welch Center for Prevention, Epidemiology, and Clinical Research, School of Medicine and Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA. ¹⁵³Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA. ¹⁵⁴Department of Endocrinology and Diabetes, Norfolk and Norwich University Hospital National Health Service Trust, Norwich, UK. ¹⁵⁵Department of Medicine, University of Kuopio and Kuopio University Hospital, Kuopio, Finland. ¹⁵⁶Faculty of Health Science, University

of Southern Denmark, Odense, Denmark. ¹⁵⁷Institute of Biomedical Science, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark. ¹⁵⁸Department of Neurology, General Central Hospital, Bolzano, Italy. ¹⁵⁹Department of Neurology, University of Lübeck, Lübeck, Germany. ¹⁶⁰Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany. ¹⁶¹Klinikum Grosshadern, Munich, Germany. ¹⁶²School of Medicine, University of Split, Split, Croatia. ¹⁶³Gen-Info Ltd., Zagreb, Croatia. ¹⁶⁴Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California, USA. ¹⁶⁵Department of Medicine, Division of Endocrinology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA. ¹⁶⁶Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA. ¹⁶⁷National Institute for Health and Welfare, Unit of Diabetes Prevention, Helsinki, Finland. ¹⁶⁸South Ostrobothnia Central Hospital, Seinajoki, Finland. ¹⁶⁹Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington, USA. ¹⁷⁰Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, NIH, Baltimore, Maryland, USA. ¹⁷¹Faculty of Medicine, University of Iceland, Reykjavík, Iceland. ¹⁷²Lab of Cardiovascular Sciences, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, USA. ¹⁷³Department of Clinical Sciences/Clinical Chemistry, University of Oulu, University of Oulu, Oulu, Finland. ¹⁷⁴National Institute of Health and Welfare, Oulu, Finland. ¹⁷⁵Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA. ¹⁷⁶MRC–Health Protection Agency Centre for Environment and Health, Imperial College London, London, UK. ¹⁷⁷UOC Geriatria, Istituto Nazionale Ricovero e cura per Anziani (INRCA) IRCCS, Rome, Italy. ¹⁷⁸These authors contributed equally to this work. Correspondence should be addressed to M.B. (boehnke@umich.edu), M.I.M. (mark.mccarthy@drl.ox.ac.uk), J.C.F. (jcflorez@partners.org) or I.B. (ib1@sanger.ac.uk).